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Bethany Crandell — 17 August 2010

Bethany Crandell — Date of Deposit

Applicant: Markou et al.	Art Unit: 1617
Serial No.: 10/527,525	Examiner: Kendra Carter
I.A. Filing Date: Sep. 10, 2003	Confirmation No.: 3218
Title: METHODS FOR TREATING DISORDERS ASSOCIATED WITH mGLU RECEPTORS INCLUDING ADDICTION AND DEPRESSION	Our Ref.: TSRI 897.1

REPLY BRIEF

MAIL STOP: Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Reply Brief is submitted in response to the Examiner's Answer, dated July 1, 2010, which was issued in connection with the appeal filed by Appellants on April 7, 2010 in the above-referenced patent application.

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I. Status of Claims

Claims 1-3, 6-7, 9-10, 14-17, 19, 27-28 and 32 are pending.

Claims 4, 5, 8, 11-13, 18, 20-26, 29-31, and 33 were canceled by Applicants

Claims 10, 14, 15, 17 and 19 are withdrawn from consideration by the Examiner

Claims 1-3, 6, 7, 9, 16, 27, 28 and 32 are rejected.

Claims 1-3, 6, 7, 9, 27, 28 and 32 are on appeal.

II. Grounds of rejection to be reviewed on appeal

Issue 1. Whether Claims 1-3, 6, 7 and 16 are unpatentable under 35 U.S.C. § 103(a) over Adam et al. (U.S. Patent No. 6,406,094; attached as Ref. 1) in view of Corsi et al. (U.S. Application 2003/0195139; attached as Ref. 2) or Chiamulera et al. (Nat. Neurosci. 4:873-874, 2001; attached as Ref. 3)?

Issue 2. Whether Claims 9, 27, 28 and 32 are unpatentable under 35 U.S.C. § 103(a) over Chiamulera et al. in view of Adam et al.?

III. Argument

A. Prior art teaching of treating withdrawal symptoms by mGluR II agonism

In the Examiner's Answer, the Examiner maintains that Adams et al. (U.S. Patent No. 6,406,094) provides a motivation to try group II mGluR antagonists in the treatment of nicotine and opiate addiction. The Examiner takes the position that the skilled artisan would be motivated by the unsubstantiated speculations of Adams et al. while disregarding the clear teaching of using group II mGluR agonists for treating addictive disorders as reported in a number of scientific publications. In support of this view, the Examiner further provided the following comments in the Examiner's Answer.

> In regards to the other art showing opposite results, the teaching of Kenny et al. can help to explain the differences. Particularly, Kenny et al. teaches on page 1075, column 1, paragraph 3, that prolonged continuous nicotine exposure increase mGluII receptor function, but decreased exposure to psychostimulants (i.e. opiates) decreased mGluII function. Thus, it is possible that chronic nicotine and psychostimulant (i.e. opiate) administration induce different alterations in glutamatergic transmission. Alternatively, this apparent discrepancy may be explained by the fact that the long-term behavioral effects of drugs of abuse are related to the dosing administration regimen. Further, although Helton et al. teaches that a mGluR II agonist treats nicotine withdrawal symptoms, Helton et al. teaches that Group II mGluR agonist decrease glutamate release (see page 1515, right column, second paragraph, last 6 lines). Helton et al. teaches that the actions of compounds such as LY354740 (the mGluR II agonist) may be altered in the nicotine-dependent animals (see page 1515, right column, last paragraph). Thus, one can not rule out suggested therapeutic teachings of Adams et al. when the effects of chronic nicotine use on mGluR agonist or nicotine modulation of glutamate excitation (i.e. regulation of glutamate release) are not known (as taught by Helton et al., page 1515, right column, first paragraph, last four lines). As the Appellants suggested on page 12 of the Appeal Brief (see paragraph 2), one would understand that inhibition of mGluR2/3 receptors to be the action of an antagonist compound. **Thus, a Group II mGluR antagonist would have the same effect as the mGluR agonist because they would both decrease glutamate**

> **release**. . . . According to the Appellant (see page 12 of the Appeal Brief, second paragraph), *Fundytus and Coderre, teach activation of the mGluR receptors could reduce withdrawal symptoms in human patients, which is in contradiction to the teachings of Helton et al. because Helton et al. teach that the agonist decreases glutamate release.* [Examiner's Answer, pages 9-10; emphases via bold and italicized fonts added]

The issue in dispute here is whether the prior art would motivate one to use Group II mGluR antagonism for treating addictive disorders. However, Appellants cannot understand how Kenny et al. and Helton et al. as discussed by the Examiner could provide any support to the Examiner's position. First, Kenny et al. is not a prior art reference. Rather, it is a post-priority publication of the present inventors which reported some of the same findings disclosed in the subject patent application. The teaching of Kenny et al. as quoted by the Examiner corresponds to the present inventors' explanation of the apparent difference between the subject disclosure (i.e., treating drug dependence via mGluRII antagonism) and the prior art teaching (i.e., treating withdrawal symptoms via mGluRII agonism). Contrary to what the Examiner apparently implied, Kenny et al. is certainly not prior art that might otherwise motivate a skilled artisan to disregard the prior art teaching of treating drug addictions via mGluRII agonism.

Turning to Helton et al., Appellants do not dispute that Helton et al. teaches that Group II mGluR agonists decrease glutamate release as pointed by the Examiner. However, contrary to the Examiner's assertion (see the bolded sentence in the above-quoted excerpt from the Examiner's Answer), a Group II mGluR antagonist and a GroupII mGluR agonist would NOT have the same effect in decreasing glutamate release. Rather, as Appellants have repeatedly pointed out, antagonism of Group II mGluR receptors (i.e., mGluR2 and mGluR3) would increase glutamate release (while blockade of Group I mGluR receptors such as mGluR5 would decrease glutamate release) (see, e.g., Appeal Brief, page 15, last paragraph). Thus, unlike what the Examiner apparently suggested, the prior art including Helton et al. would not motivate

one to substitute a Group II mGluR antagonist for the Group II mGluR agonist used in Helton et al.

Fundytus and Coderre (Brit. J. Pharmacol. 121:511-4, 1997) similarly taught treating withdrawal symptoms with a Group II mGluR agonist. Just like the Group II mGluR agonist used in Helton et al., the Group II mGluR agonist in Fundytus and Coderre would also be expected to decrease glutamate release. Contrary to what the Examiner appears to believe (see the italicized sentence in the above-quoted excerpt from the Examiner's Answer), Fundytus and Coderre did not teach or suggest that the employed Group II mGluR agonist led to an increase of glutamate release. Therefore, the teaching of Fundytus and Coderre is entirely consistent with the teaching of Helton et al. In other words, both Helton et al. and Fundytus and Coderre taught treating withdrawal symptoms via a Group II mGluR agonist. They would by no means motivate one to use a Group II mGluR antagonist to treat the same disorder.

Finally, Appellants could not see any relevance of the other teachings of Helton et al. to the issue of whether the prior art taught or suggested treating withdrawal symptoms via Group II mGluR antagonism. For example, the last three paragraphs of Helton et al. as referred to by the Examiner merely discussed possible underlying mechanisms of the observed effect of the Group II mGluR agonist in ameliorating withdrawal symptoms. The authors pointed out that there is much unknown about how the agonist compound attenuated the nicotine withdrawal symptoms, e.g., its binding sites in the brain and the cellular mechanism of its action. However, these discussions surely did not cast any doubt on the observed effect itself, let alone providing any suggestion to use an opposite compound, i.e., a Group II mGluR antagonist, in the hope of achieving the same effect.

B. Teaching away by Fundytus et al. (Brit. J. Pharmacol. 120:1015-20, 1997)

Regarding Fundytus et al. (Brit. J. Pharmacol. 120:1015-20, 1997), Appellants have previously clarified that Figure 1 of this reference showed that the non-selective mGluR antagonist α-methyl-4-carboxyphenylglycine (MCPG) prevented development of

morphine dependence in normal rats (Figure 1 of Fundytus et al.). On the other hand, Figure 2 of Fundytus et al. clearly indicated that this compound has no effect in treating withdrawal symptoms in rats that have already developed dependence. In the Examiner's Answer, the Examiner acknowledged that Figure 2 of Fundytus et al. showed that the compound has no effect in treating withdrawal symptoms in addicted/dependent subjects (see the Examiner's Answer, page 12, first full paragraph). However, the Examiner nonetheless asserted that Figure 1 of Fundytus et al. indicates that the compound was effective in treating withdrawal symptoms in "an existing addictive/dependent disorder". In reply, Appellants provide the following clarifications to further illustrate the Examiner's incorrect interpretation of Fundytus et al. as it is applied towards the rejections of the presently appealed claims.

Appellants note that, in maintaining the position that Figure 1 of Fundytus et al. taught treatment of withdrawal symptoms, the Examiner's Answer ignored or failed to reconcile the different conclusion that Fundytus et al. drew from the results reported in Figure 2. To reiterate the irrelevance of Figure 1 of Fundytus et al. to Appellants' claims, Appellants wish to stress again that the claimed invention is directed to treating subjects that have already developed drug dependence, and that the subjects are administered with the recited mGluR antagonist compounds to ameliorate/reduce withdrawal symptoms which will manifest upon cessation of drug use. The subjects are not administered with the mGluR antagonist compounds while still undergoing drug use. On the other hand, as clearly explained in the Appeal Brief (e.g., pages 17-18), the rats employed in the study of Figure 1 of Fundytus et al. are normal rats which were chronically administered morphine and at the same time treated with the mGluR antagonists. The goal of the study was to determine whether the compound can prevent the normal rats from developing morphine dependence. Regardless of how these rats were termed in Fundytus et al. (e.g., "morphine -dependent rats"), the simple facts remain to be that the rats are not subjects which have already developed drug dependence prior to administration of the compound, and that the mGluR antagonist

compound was not administered to the rats after morphine infusion is stopped.

As further clarification, Appellants note that withdrawal symptoms were assessed in the studies reflected in both Figure 1 and Figure 2 of Fundytus et al. However, the purpose of the assessment in the study of Figure 1 was to determine whether the rats have developed drug dependence (as evidenced by the presence of withdrawal symptoms when the drug is stopped), i.e., whether the rats display withdrawal symptoms. On the other hand, assessment of withdrawal symptoms in the study of Figure 2 was to examine whether the administered compound could ameliorate the withdrawal symptoms already present in the dependent rats, i.e., whether there is a reduction in the severity of withdrawal symptoms. It is the study shown in Figure 2, not Figure 1, of Fundytus et al. which might be relevant to Appellants' invention. The results shown in Figure 2 of Fundytus et al. unequivocally indicate that the non-selective mGluR antagonist had no effect to treat withdrawal symptoms in rats that have already developed dependence.

IV. Conclusion

Appellants submit that the other points of argument that were raised in the Examiner's Answer are repetitive, and thus were fully addressed in Appellants' previously filed Appeal Brief and the instant Reply Brief.

For all the reasons set forth herein and in the Appeal Brief, Appellants respectfully request that the rejections under 35 U.S.C. § 103(a) of claims 1-3, 6, 7, 9, 16, 27, 28 and 32 be reversed, and that this patent application be remanded back to the Examiner for further processing.

If there are any fees associated with this Appeal Brief, please charge our Deposit Account No. 19-0962.

Respectfully submitted,

8/17/2010

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V. Claims Appendix

1. (previously presented) A method for treating drug dependence in a subject, comprising administering to a subject with drug dependence an effective amount of (a) a first antagonist which modulates metabotropic glutamate receptor 2 and/or metabotropic glutamate receptor 3, and (b) a second antagonist which modulates metabotropic glutamate receptor 5, thereby treating the disorder; wherein the drug dependence is selected from the group consisting of nicotine addiction, alcohol addiction, opiate addiction, amphetamine addiction, cocaine addiction, and methamphetamine addiction.

2. (previously presented) A method for treating drug dependence in a subject, comprising administering to a subject with drug dependence an effective amount of (a) a first antagonist which modulates metabotropic glutamate receptor 2, and (b) a second antagonist which modulates metabotropic glutamate receptor 5, thereby treating the disorder; wherein the drug dependence is selected from the group consisting of nicotine addiction, alcohol addiction, opiate addiction, amphetamine addiction, cocaine addiction, and methamphetamine addiction.

3. (previously presented) A method for treating drug dependence in a subject, comprising administering to a subject with drug dependence an effective amount (a) a first antagonist which modulates metabotropic glutamate receptor 3 and (b) a second

antagonist which modulates metabotropic glutamate receptor 5, thereby treating the disorder; wherein the drug dependence is selected from the group consisting of nicotine addiction, alcohol addiction, opiate addiction, amphetamine addiction, cocaine addiction, and methamphetamine addiction.

4-5. (canceled)

6. (previously presented) The method of claim 1, wherein the drug dependence is nicotine addiction.

7. (previously presented) The method of claim 1, wherein the drug dependence is cocaine addiction.

8. (canceled)

9. (previously presented) The method according to claim 1, wherein the antagonist which modulates metabotropic glutamate receptor 5 is 2-methyl-6-(phenylethynyl)-pyridine, and the antagonist which modulates metabotropic glutamate receptor 2 and/or metabotropic glutamate receptor 3 is 2S-2-amino-2-(1S,2S-2-carboxycyclopropan-1-yl)-3-(xanth-9-yl)propionic acid .

10. (withdrawn) A combination comprising (a) at least a first active ingredient selected from a metabotropic glutamate receptor 2 antagonist and a metabotropic glutamate receptor 3 antagonist, and (b) at least a second active ingredient being a metabotropic glutamate receptor 5 antagonist, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt, and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

11-13. (canceled)

14. (withdrawn) The combination according to claim 10 which is a combined preparation or a pharmaceutical composition.

15. (withdrawn) The combination according to claim 10 for simultaneous, separate or sequential use in the treatment of an addictive disorder or depression.

16. (previously presented) A method of treating a warm-blooded animal having an addictive disorder comprising administering to the animal a combination according to claim 10 in a quantity which is jointly therapeutically effective against an addictive disorder and in which the compounds can also be present in the form of their pharmaceutically acceptable salts; wherein the addictive disorder is selected from the

group consisting of nicotine addiction, alcohol addiction, opiate addiction, amphetamine addiction, cocaine addiction, and methamphetamine addiction.

17. (withdrawn) A pharmaceutical composition comprising a quantity, which is jointly therapeutically effective against an addictive disorder or depression, of a pharmaceutical combination according to claim 10 and at least one pharmaceutically acceptable carrier.

18. (canceled)

19. (withdrawn) A commercial package comprising a combination according to claim 10 together with instructions for simultaneous, separate or sequential use thereof in the treatment of an addictive disorder.

20-26. (canceled)

27. (previously presented) A method for treating an addictive disorder, comprising: a) administering to a subject in need thereof, an effective amount of a first antagonist that modulates mGluR5 during a first time period, wherein the first time period is a time period wherein the subject expects to be in an environment wherein, or exposed to stimuli in the presence of which, the subject habitually uses an addictive substance; and

b) administering a second antagonist that modulates mGluR2 and/or 3 during a second time period, wherein the second time period is a time period wherein the subject is suffering from withdrawal; wherein the addictive disorder is selected from the group consisting of nicotine addiction, alcohol addiction, opiate addiction, amphetamine addiction, cocaine addiction, and methamphetamine addiction.

28. (previously presented) The method of claim 27, wherein the antagonist that modulates mGluR5 is 2-methyl-6-(phenylethynyl)-pyridine and the antagonist that modulates mGluR2 and/or 3 is 2S-2-amino-2-(1S,2S-2-carboxycyclopropan-1-yl)-3-(xanth-9-yl)propionic acid.

29-31. (canceled)